REMARKS

Claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202 were previously withdrawn from this application. Claims 119, 124, 127, 128, 152, 153, 170, 178-182, 186, 188, 192-196, 199 and 203-205 were previously cancelled. Applicants reserve the right to file continuation or divisional applications directed to the cancelled or withdrawn subject matter. Claims 6, 11, 54, 59, 97 and 191 are currently amended. Support for the amendments can be found throughout the specification, specifically in the claims as originally filed. No new matter has been added. Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125, 126, 151, 157, 161-169, 184 and 191 are currently pending.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 6 is rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner states that it is unclear whether the phrase "wherein the result comprises changes in cytokine responses" results from the administration of intermediary metabolite or the pathogenesis of the disease. *See* Office Action page 2. Claim 6 has been amended to recite "...wherein the result of said administration comprises..." Withdrawal of the rejection is respectfully requested.

Claims 49, 50, 51 and 52 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner states that it is unclear whether the phrase "wherein the result comprises changes in cytokine responses" results from the administration of intermediary metabolite or the pathogenesis of the disease. *See* Office Action page 3. Applicants respectfully disagree. Independent claim 43 (from which claims 49, 50, 51 and 52 depend) reads in pertinent part "...the result *of said administration* comprising a change in the number or function of regulatory, immuno-regulatory or NKT cells." Thus, the recitation of the word "result" in claims 49 ("...wherein said *result* further comprises changes in cytokine responses") and 52 ("...wherein said *result* further comprises changes in the Th1/Th2 balance...) finds antecedent basis in claim 43 and clearly refers to the result of the administration of the intermediary metabolite. Withdrawal of the rejection is respectfully requested.

Claims 161, 163, 165 and 167 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for reasons similar to the rejection of claims 49, 50, 51 and 52. *See* Office Action pages 3-4. Applicants respectfully direct the Examiner's attention to the wording of claim 44 (from which claims 161, 163, 165 and 167 depend) which reads in pertinent part "...the result *of said administration* comprising the reduction, inhibition, or decrease of the number or function of regulatory, immuno-regulatory or NKT cells." Thus, the recitation of the word "result" in claims 161 ("...wherein said *result* further comprises changes in cytokine responses") and 163 ("...wherein said *result* further comprises changes in the Th1/Th2 balance...) finds antecedent basis in claim 44 and clearly refers to the result of the administration of the intermediary metabolite. Withdrawal of the rejection is respectfully requested.

Claims 162, 164, 166 and 168 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for reasons similar to the rejection of claims 49, 50, 51 and 52. *See* Office Action page 4. Applicants respectfully direct the Examiner's attention to the wording of claim 45 (from which claims 161, 163, 165 and 167 depend) which reads in pertinent part "...the result *of said administration* comprising the stimulation or increase of the number or function of regulatory, immuno-regulatory or NKT cells." Thus, the recitation of the word "result" in claims 162 ("...wherein said *result* further comprises changes in cytokine responses") and 164 ("...wherein said *result* further comprises changes in the Th1/Th2 balance...) finds antecedent basis in claim 45 and clearly refers to the result of the administration of the intermediary metabolite. Withdrawal of the rejection is respectfully requested.

Claim 191 is rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner states that the limitation of "manipulation" in line 3 lacks antecedent basis. *See* Office Action page 5. Claim 191 has been amended to recite "...administration, treatment or modulation." Antecedent basis for the term "modulation" may be found in claim 60. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(b)

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 97, 120, 125, 151, 157, 161-169, and 184 are

rejected under 35 U.S.C. §102(b) as being anticipated by Marinier *et al.* (U.S. Patent No. 5,747,463; hereinafter "Marinier"). The Examiner states that Marinier teaches the treatment of a disease in a mammalian subject comprising administering an effective amount of a mammalian intermediary metabolite comprising a glycolipid, wherein the pathogenesis of the disease is derived from an inflammatory immune response. See Office Action page 5. The Examiner further notes that "...the limitations of many instant claims, including claims 47-52, are not active steps in the claims, but only the mechanism of action which occur by the series of active steps in the claims." *See* Office Action page 6. The Examiner then concludes that since Marinier teaches the same active steps, the same mechanism of action must also occur. *Id.*

Marinier describes a class of malonate compounds which are derivatives of glycolipids. These compounds inhibit selectin-mediated cellular adhesion for the treatment of certain diseases in mammals. The family of compounds described in Marinier may be clearly differentiated from the compounds that are the subject of the present claims. In all cases, the present claims comprise the use of a compound that embraces two limitations: the compound must consist of a "lipid or glycolipid" and the compound must be a "mammalian intermediary metabolite". While the compounds described in Mariner may be chemically classified as glycolipids, these compounds would not fulfill the limitation of a "mammalian intermediary metabolite". The present application is a continuation-in-part of US Application 10/375,906 which was incorporated by reference. The '906 application was later published as U.S. Patent Application Publication No. 2004/0171522, as cited in the remainder of this paper. The '522 publication defines an intermediary metabolite as follows: "In the present invention, metabolites or intermediary metabolites are considered to be products of enzymatic processes in a mammalian system." *See* paragraph [0021]. Thus, a mammalian intermediary metabolite is a product that in its natural state is present in a mammalian cell. The existence of such compounds as a natural element in a mammalian cell is further enunciated later in paragraph [0021] with the statement "Furthermore, such **elevated** levels of metabolites could also be obtained in the subject indirectly, either through enhancement of synthesis of the compound or inhibition of the degradation of the compound." (emphasis added). Applicants assert that the term "elevated" has an implicit meaning of the existence of a basal level of the metabolite in a cell that is then raised

by enhancement of synthesis or inhibition of degradation.

In contrast, the artificial nature of the Marinier compounds is repeatedly discussed in the specification of the '463 patent.:

"There is provided a **novel** series of malonate derivatives of glycolipid compounds…." (emphasis added). *Abstract.*

"The present invention provides a **novel** series of malonate derivatives of glycolipid compounds." (emphasis added). Col. 1, lines 15-16.

"The present invention provides **novel** O-dicarboxyalkylated glycolipids…." (emphasis added). Col. 2, line 52.

"The present invention provides **novel** O-dicarboxyalkylated α and β glycolipid compounds…." (emphasis added). Col. 3, lines 5-6.

Quite clearly, the **novel** compounds described by Marinier are not mammalian intermediary metabolites as they are new compounds that are not found in nature (particularly in mammalian cells). The novelty of these compounds is further evidenced by the fact that composition claims for these compounds were allowed in the Marinier patent.

To support a rejection under Section 102, an Examiner must show that each and every element recited in the claimed invention is taught by a single reference. MPEP § 2131. The present claims require the administration of an effective amount of a mammalian intermediary metabolite. The compounds described in Marinier are not mammalian intermediary metabolites as defined by the present specification because they are not naturally occurring. Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 97, 120, 125, 151, 157, 161-169, and 184 are clearly novel over Marinier. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

Marinier in view of Das

Claims 75, 109 and 126 are rejected under 35 U.S.C. §103(a) as being obvious over Marinier as applied above and further in view of Das (U.S. Patent No. 5,869,048; hereinafter "Das"). The Examiner concedes that Marinier does not teach administration of an antigen associated with colitis, but states that Das satisfies this deficiency by teaching a method of

vaccinating a human against ulcerative colitis by administrating a colonic antigen. *See* Office Action page 7. The Examiner then concludes that it would have been obvious to combine the references because of the advantages of vaccinating a subject. *Id.*

Applicants respectfully traverse the rejection and assert that the Examiner has not shown that claims 79, 109 and 126 are obvious over the combination of Marinier and Dias. As discussed above, Marinier does not disclose mammalian intermediary metabolites. Dias does not cure the deficiencies of Marinier. Das discloses a method of treating ulcerative colitis by administration of an antibody which binds to the colonic antigen of ulcerative colitis. There is no description in Das of mammalian intermediary metabolites. In addition, the present claims require compositions comprising lipids or glycolipids. Das teaches away from the present invention by disclosing a method utilizing an antibody. Thus, the combination of the cited references does not result in the methods of the currently claimed invention, i.e., a method for the treatment of a disease by administration of a mammalian intermediary metabolite wherein the intermediary metabolite is a lipid or glycolipid. There is no motivation to combine the references and there would be no expectation of success that the combination of the references would result in Applicants currently claimed method of treatment. Withdrawal of the rejection is respectfully requested.

Marinier in view of Collins and Liotta

Claims 54, 76 and 191 are rejected under 35 U.S.C. §103(a) as being obvious over Marinier as applied above and further in view of Collins *et al.* (U.S. Patent Application Publication No. 2002/0141977; hereinafter "Collins") and Liotta *et al.* (U.S. Patent No. 6,610,835; hereinafter "Liotta"). The Examiner concedes that Marinier does not teach administration of a dendritic cell to a subject that has not been without food for a minimum of 12 hours. The Examiner contends that Collins teaches an immuno-therapy method comprising administration of antigen presenting cells (including dendritic cells) for the treatment of disease, while Liotta teaches that sphingolipids are found in a number of foods. *See* Office Action pate 8. The Examiner then concludes that it would have been obvious to combine the references because one of ordinary skill in the art would have been motivated to use dendritic cells for the advantage

of providing a known method of immunotherapy. *Id.*

Applicants respectfully traverse the rejection. As discussed in detail above, Marinier does not teach mammalian intermediary metabolites for the treatment of a disease. Collins teaches dendritic cells which have been exposed to bacterial antigens. These cells may then be utilized for the prevention or treatment of diseases, such as inflammatory diseases. As with Marinier, there is no teaching or suggestion in Collins of the use of mammalian intermediary metabolites for the treatment of disease.

Liotta also does not cure the deficiencies of Marinier. The Liotta specification reads at Col. 8, lines 16-21:

> ...it would be of benefit to provide new sphingolipid derivatives that improved properties, bioavailability, or are targeted to desired locations for effective therapy. It is therefore an object of the present invention to provide new sphingolipids ....

Liotta clearly contains no teaching of administration of mammalian intermediary metabolites, even in the form of sphingolipids. To the contrary, Liotta teaches only that such natural forms of sphingolipids are inadequate. Liotta discloses the use sphingolipid derivatives, *i.e. artificial* analogues of the natural sphingolipids found in mammalian cells. The compositions taught by Liotta are not identical or substantially identical to natural mammalian sphingolipids.

Contrary to the Examiners assertion on page 8 of the Office Action, the combination of the references provides no teaching of administration of a mammalian intermediary metabolite. None of the references encourages the use of a normal mammalian intermediary metabolite, but instead only encourages the use of non-natural products which would not normally be found within a mammalian cell. A person of skill in the art would have no motivation to combine references because the combination does not result in Applicants presently claimed invention. The withdrawal of the rejection of claims 54, 76 and 191 is respectfully requested.

Double Patenting

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 120, 125-126, 151, 157, 161-169, 184 and 191 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-15 of copending Application No. 11/378,941.

As this is a provisional rejection, Applicants respectfully request the rejection be held in abeyance until the finding of allowable subject matter.

Conclusion

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

The Examiner is invited to contact the undersigned at 412-918-1100 to discuss any matter concerning this application.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the deposit account number 50-0525.

Respectfully submitted,

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